REMARKS

Upon entry of this amendment, claim 16 will be amended, whereby claims 13-19 and 26-28 will remain pending, with claims 13, 15 and 17-19 being independent claims.

Claim 16 has been amended herein to change its dependency from claim 17 to previous claim 15 in response to the objection to claim 16. Therefore, this amendment is being made to advance prosecution of the application by reducing issues, and is properly entered after final rejection.

Reconsideration and allowance of the application are respectfully requested.

Consideration of Third Supplemental Information Disclosure Statement

Applicants express appreciation for the inclusion with the Office Action of an initialed copy of the Form PTO-1449 submitted with the Third Supplemental Information Disclosure Statement filed November 30, 2006, whereby the Examiner's consideration of the Third Supplemental Information Disclosure Statement is of record.

Response To Objection Of Claim 16

In response to the objection of claim 16 for depending upon a later numbered claim, claim 16 has been amended to be dependent upon claim 15. Accordingly, this ground of objection should be withdrawn.

Response To Rejections

The following rejections are set forth in the Final Office Action:

(a) Claims 13-19 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welter et al. (U.S. Patent No. 4,418,069), or Dereu et al. (U.S. Patent No. 4,730,053), or EP 0 366 990, or CA 0227898, or WO 97/26968.

The rejections contend that:

As explained in the previous office action, all these articles expressly teach administration of structurally similar compounds in vivo to achieve the same effect as claimed here in–vitro. Inasmuch as the in-vivo administration is taught achieving reduction of the substrate, it is expected that in vitro effect will be achieved in the same way, absent evidence to the contrary.

In response to these grounds of rejection, Applicants note that the rejection is without appropriate basis in that the rejection improperly utilizes Applicants' disclosure, and not the prior art, as the supporting reasoning for the rejection. The rejection contends that the documents disclose that, "the in-vivo administration is taught achieving reduction of the substrate"; however, the rejection does not point to any disclosure in any of the documents that discloses ebselen reduction of the substrate. The documents disclose:

(a) benzisoselenazolones and the *in vivo* treatment of rheumatic and arthritic diseases using benzisoselenazolones (Welter et al.);

(b) S-(Carbamoyl-phenylselenyl) derivatives of mercaptanes of the discloses general formula (I), and to an *in vivo* process for the treatment of diseases caused by cell injury due to the increased formation of active oxygen metabolites (Dereu et al.);

(c) stable parenteral solutions of 2-phenyl-1,2-benzisoselenazol-3(2H)-one with a discussion of uses of ebselen in treatment of numerous diseases, such as the prophylaxis and therapy of infection diseases, the therapy of malignant tumors, therapy of rheumatic diseases,

therapy of deficiencies caused by oxidative stress, an the topical treatment of inflammatory and allergic skin diseases such as psoriasis (EP 0 366 990);

(d) a cyclooxygenase-2-inhibitor and treatment of therapy and/prophylaxis of such diseases which are caused in a disturbance and/or in an influence of the cyclooxygenase –2-inhibition with a peroral administration disclosed (CA 0227898); and

(e) treatment of asthma by administering to a mammal 2-phenyl-1,2-benzoisoselenazole-3(2H)-one or a pharmaceutically acceptable salt thereof (WO 97/26968).

There is no teaching in any of the documents utilized in the rejections of achieving reduction of a substrate. This is part of Applicants' disclosure, and cannot be utilized to support a rejection. The rejections must establish that one having ordinary skill in the art, from knowledge within the prior art, would have arrived at the subject matter recited in Applicants' claims.

Additionally, the Examiner is reminded of the arguments previously advanced in their Appeal Brief, filed April 24, 2004, such as beginning at page 12, wherein it is noted that ebselen is expected to be an inhibitor of thioredoxin reductase. In this regard, the Examiner's attention is once again directed to Engman et al., "Diaryl chalcogenides as selective inhibitors of thioredoxin reductase and potential antitumor agents", Anticancer Res. 1997 Nov-Dec;17(6D):4599-605. From a review of this document, it can be seen that Engman as well as Arteel (which is once again used in a rejection of the claims and will be argued below) do not disclose the use of ebselen as a substrate for thioredoxin reductase. Applicants once again note that in its results and discussion, at page 268, right column, at the top of the column, Arteel cites Engman (Reference No. 22) for its disclosure of **ebselen being an inhibitor of thioredoxin reductase**, and discusses a mechanism that is not in conformance with that of the presently disclosed and claimed invention.

Thus, the prior art shows ebselen as being an inhibitor and not a substrate, which is in contrast with the Examiner's supporting assertion for the rejections. Therefore, the obviousness rejections based upon each of Welter et al., or Dereu et al., or EP 0 366 990, or CA 0227898, or WO 97/26968 is without appropriate basis, and should be withdrawn. If the rejections are maintained, the Examiner is respectfully requested to fully explain and provide support for the assertions made in the rejections.

Accordingly, the rejections of record should be withdrawn.

(b) Claims 13-19 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Arteel et al. (Chem. Res. Toxicol, 1999), Bjornstedt et al. (JBC, 1995), and Kumar et al. (Eur. J. Biochem, 1992) and in view of Muller et al. (Biochem. Pharmac. 3235-3239, 1984) and Schewe (Gen. Pharmac. Vol. 26, pp. 1153-1169, 1995).

In this ground of rejection, it is contended that "It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the process of Arteel et al, and Bjornstedt et al, wherein in vitro experiment is expressly done using NADPH, selenocystine and thioredoxin similar to claimed herein, by using ebselen, as taught by Muller et al and Schewe, because the latter references are expressly teaching that ebselen mimics glutathione peroxidase like activities, and Kumar et al is expressly teaching that selenite is a substrate for thioredoxin reductase and NADPH, and Bjornstedt et al expressly teaching that selenium is an essential element to have anti oxidant property, ebselen is having glutathione peroxidase like activity in vitro, it is obvious that ebselen when reacted with thioredoxin reductase and NADPH, would result in a method similar to claimed herein, absent evidence to the contrary.

The rejection further contends that, "Thus, as noted in the rejection, Bjornstedt does not disclose method as recited in Applicants' claims which include the recited compounds let alone teach or suggest that compounds having a structure as ebselen would be a substrate, an inhibitor or most likely not show any reactivity."

The rejection further contends referring to Bjornstedt, ".....it is selenium which is important part of the reaction and other reference are expressly teaching that selenium is active part, and Muller is teaching ebselen to be behaving like glutathione peroxidase like activity, thus suggesting similar process as claimed herein."

Still further, referring to Kumar et al., the rejection notes that the structure is different but contends that, "it is selenium that is important and the references are expressly teaching equivalence of selenite, ebselen having glutathione peroxidase like activity."

Regarding Arteel not using ebselen, the rejection again asserts that, "it is selenium which is important and inasmuch as ebselen is taught in a similar glutathione peroxidase like activity , the method claim is obvious as a whole, absent evidence to the contrary.

Initially, Applicants again note, as set forth above, that the prior art shows ebselen as being an inhibitor and not a substrate. Therefore, the assertions in the rejection that it is selenium that is important and the references expressly teaching that selenium is active part is without appropriate basis. The rejection does not address that the prior art, such as Arteel and the cited Engman article specifically disclose that ebselen is an inhibitor. The contention set forth in the rejection that it is selenium that is important is like saying that any compound that contains carbon would be useful to cure a disease merely because one compound capable of curing the disease contains carbon.

Still further, Applicants submit that the rejection is not clear as to how the documents are being combined. What is meant by the combined teachings of Arteel, Bjornstedt, and Kumar. Moreover. how can the various disclosures be combined, and how can Applicants' process be arrived at when Arteel discloses that ebselen is an inhibitor? Certainly, the rejection must address this issue and, as noted above, cannot utilize Applicants' disclosure to support the rejection.

Moreover, Applicants again note that, as disclosed in Bjornstedt at page 11761, right column, third full paragraph, Bjornstedt is directed to the investigation of whether thioredoxin reductase and thioredoxin can reduce lipid hydroperoxides and if low molecular weight selenium compounds could act as charge transfer catalysts. Bjornstedt discloses that this could be an important alternative pathway for the detoxification of hydroperoxides in addition to GSH-Px-mediated reduction. Thus, as noted in the rejection, Bjornstedt does not disclose methods as recited in Applicants' claims which include the recited compounds let alone teach or suggest that compounds having a structure such as ebselen would be a substrate, an inhibitor or most likely not show any reactivity. In fact, ebselen is not a substrate for a majority of the world's thioredoxin reductases found in all bacteria, plants, yeast, etc. These thioredoxin reductases do not reduce ebselen and, in fact, ebselen acts as an inhibitor.

Regarding Kumar, Applicants again note that Kumar relates to the fact that sodium selenite is a redox cycling agent, and does not disclose methods as recited in Applicants' claims which include the recited compounds let alone teach or suggest that compounds having a structure such as ebselen would be a substrate, an inhibitor or most likely not show any reactivity.

Applicants remind the Examiner that Arteel does not teach any methods wherein ebselen is used as a substrate for thioredoxin reductase. Arteel performs experiments with respect to the activity of mammalian thioredoxin reductase using a peroxynitrite reductase. Thus, at page 264, at the bottom of the left-hand column, Arteel discloses, "Here we investigated whether mammalian TR [thioredoxin reductase] can function as a peroxynitrite reductase." In performing the study, as disclosed in the Results section at page 265, left-hand column, Arteel infuses peroxynitrite to maintain a 0.2 pM steady-state concentration in potassium phosphate buffer. Arteel uses benzoate hydroxylation and nitrite formation as indices of oxidation reactions of peroxynitrite and of peroxynitrite reduction. Arteel particularly notes that when selenocystine or ebselen are present in the reaction mixture, there is a significant suppression of benzoate hydroxylation and an increase in nitrite formation until the NAPDH was oxidized. Arteel particularly specifies that the addition of thioredoxin did not enhance these effects (page 264, in the Abstract). Moreover, on page 265, right-hand column, Arteel discloses that. "Addition of TR to ebselen had no effect under these conditions (Y)."

Therefore, Arteel should be considered to be nonenabling for processes wherein thioredoxin is present as Arteel does not teach or suggest any need for having the thioredoxin present in the reaction.

Applicants further note that as discussed in its previous responses the prior art at most teaches that ebselen is an inhibitor of thioredoxin reductase, and that ebselen selenoxide can be a substrate. However, Applicants' claims do not include ebselen selenoxide. Arteel shows no effect of thioredoxin on reduction of ebselen selenoxide by NADPH and thioredoxin reductase.

The Examiner is reminded that in contrast to the prior art of record, the present invention recognizes and demonstrates that ebselen is a substrate being reduced by NADPH and thioredoxin reductase with a low Km-value meaning that it is a very good substrate undergoing unlimited cycles of oxidation/reduction in the presence of hydrogen peroxide without affecting the activity of the enzyme. The reduced ebselen is called ebselen selenol and has the Se-N bond broken by reduction. The selenol is oxidized back to ebselen by hydrogen peroxide or another peroxide and a new cycle starts. The reaction is ultimately driven by NADPH. Reduced thioredoxin strongly enhances the thioredoxin reductase reaction which is also proven by determination of the rate of reduction of ebselen by reduced thioredoxin using kinetics with tryptophan fluorescence. The result, never seen before, is that ebselen is a very efficient oxidant of reduced thioredoxin.

Thus, Applicants submit that it is by no means clear that ebselen would be a substrate for thioredoxin or thioredoxin reductase following any disclosure in Arteel, or any of the other documents utilized in the rejection. The substrate used in Arteel's work is selenocysteine, which is different from the selenocystine of Bjornstedt.

Applicants respectfully submit that one having ordinary skill in the art would not have found it obvious to have combined the disclosures to arrive at the claimed subject matter. There is no teaching or suggestion in the documents utilized in the rejection that mammalian thioredoxin reductase is a selenoenzyme and there is therefore no possibility of deducing that ebselen would be a substrate. In fact, most people testing thioredoxin reductase at the time of Applicants' invention would buy the bacterial enzyme, which was commercially available from IMCO in Stockholm as the only source and they would have seen no reactions with ebselen. Applicants' experiments utilized preparations of mammalian thioredoxin reductase from human placenta or calf thymus and with that

Applicants observed that ebselen is a substrate. An extremely fast reaction with thioredoxin was part of Applicants' findings.

Muller and Schewe are utilized in the rejection for the assertion that they disclose that ebselen mimics glutathione peroxidase. While it may be true that ebselen mimics glutathione peroxidase, that is not a major concern relative to Applicants' recited methods as the issue relates to the fact that one having ordinary skill in the art at the time of Applicants' invention would not have knowledge of ebselen being a thioredoxin reductase substrate, or a thioredoxin oxidant.

If the rejection is maintained, the Examiner is requested to specifically point out supporting disclosure for the rejection in the documents utilized in the rejection, which documents include as an author one of the coinventors of the present application, i.e., Arne Holmgren, who is a co-author of Bjornstedt and Kumar.

Accordingly, the rejections of record are without appropriate basis, and should be withdrawn.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
Arne HOLMGREN et al.

Bruce H. Bernstein
Reg. No. 29,027

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GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

Arnold Turk
Reg. No. 33094